Clinical Outcome of Patients With Advanced Coronary Artery Disease After Viability Studies With Positron Emission Tomography

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Objective. The aim of this study was to determine the prognostic significance of perfusion-metabolism imaging in patients undergoing positron emission tomography for myocardial viability assessment.

Background. Positron emission tomography using nitrogen-13 ammonia and [18]fluorodeoxyglucose to assess myocardial blood flow and metabolism has been shown to predict improvement in wall motion after coronary artery revascularization. The prognostic implications of metabolic imaging in patients with advanced coronary artery disease have not been investigated.

Methods. Eighty-two patients with advanced coronary artery disease and impaired left ventricular function underwent positron emission tomographic imaging between August 1988 and March 1990 to assess myocardial viability before coronary artery revascularization.

Results. Forty patients underwent successful revascularization. Patients who exhibited evidence of metabolically compromised myocardium by positron emission tomography (decreased blood flow with preserved metabolism) who did not undergo subsequent revascularization were more likely to experience a myocardial infarction, death, cardiac arrest or late revascularization due to development of new symptoms than were the other patient groups ($p < 0.01$). Concordantly decreased flow and metabolism in segments of previous infarction did not affect outcome in patients with or without subsequent revascularization. Those with a compromised myocardium who did undergo revascularization were more likely to experience an improvement in functional class than were patients with preoperative positron emission tomographic findings of concordant decrease in flow and metabolism.

Conclusions. Positron emission tomographic myocardial viability imaging appears to identify patients at increased risk of having an adverse cardiac event or death. Patients with impaired left ventricular function and positron emission tomographic evidence for jeopardized myocardium appear to have the most benefit from a revascularization procedure.

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Positron emission tomography has evolved as a new imaging modality with many potential clinical and research applications in cardiology. Clinical studies (1-12) have suggested that it may be useful in the noninvasive diagnosis of coronary artery disease (1-5), assessment of physiologic severity of stenosis (2,3,5), imaging of myocardial infarcts (6-10) and determination of myocardial viability (7-9,11,12) and the effects of intervention on myocardial blood flow, metabolism and function (12). Although primarily employed as a sophisticated research tool, this technique has demonstrated clinical utility in the preoperative assessment of patients with advanced coronary artery disease and impaired left ventricular function considered for coronary artery revascularization. The combined evaluation of regional myocardial blood flow and glucose metabolism has allowed identification of specific metabolic patterns that occur in ischemically compromised but viable myocardium (13,14) as well as in scar tissue. Maintained glucose metabolism as evidenced by myocardial [18]fluorodeoxyglucose uptake in segments with reduced blood flow has been considered as a scintigraphic hallmark of viable myocardium, whereas concordant decrease of flow and metabolism is considered specific for scar tissue.

Previous studies (12) using positron emission tomography and the glucose analogue F-18 deoxyglucose examined regional left ventricular wall motion before and after surgical revascularization and correlated these findings with preoperative metabolic imaging. Abnormal wall motion was predicted to be reversible in regions in which positron emission tomography showed preserved F-18 deoxyglucose uptake and was predicted to be irreversible in regions with depressed F-18 deoxyglucose uptake. With use of these criteria, 75% to 85% of myocardial segments with maintained F-18 deoxyglucose uptake were correctly identified as salvageable, and 78% to 92% of myocardial segments without evidence of metabolic activity (12,15,16) did not recover.

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Although metabolic imaging with positron emission tomography has been shown to accurately predict wall motion recovery after revascularization, its prognostic utility, independent of treatment strategies, has not yet been established. The aim of this study was to determine whether the identification of jeopardized myocardium with positron emission tomography predicts subsequent cardiac events and whether revascularization affects the clinical outcome in patients with advanced coronary artery disease and impaired left ventricular function. We also examined the relation between scintigraphic results and subsequent change in functional status in this patient group.

Methods

Study patients. A retrospective analysis of all patients who had undergone positron emission tomographic myocardial viability scanning at the University of Michigan between August 1988 and March 1990 was performed. All patients had known coronary artery disease and had undergone positron emission tomographic imaging to assess myocardial viability before coronary artery revascularization. All were considered to be candidates for surgical revascularization or percutaneous transluminal coronary angioplasty and had a decreased left ventricular ejection fraction and at least one major vessel with significant stenosis. Patients were included in the study if their chart was available for review and telephone contact was established with the patient or his or her representative. One hundred ten patients underwent positron emission tomographic viability studies during this time interval. Because of geographic considerations, complete data acquisition was not possible in 23 patients referred for viability studies from outside facilities, and these patients were not included in the analysis. An additional five patients were later withdrawn because of elective heart transplantation in three and poor F-18 deoxyglucose scans that prevented adequate data interpretation in two.

Positron emission tomographic imaging. All patients were studied in the postprandial state after additional oral glucose loading with 50 g of glucose. Initial transmission scanning for attenuation correction was performed followed by myocardial perfusion imaging using either ^{13}N-labeled ammonia or ^{82}rubidium. After tracer decay, 10 mCi of F-18 deoxyglucose was injected and data acquisition started 40 min after tracer injection. After the administration of flow and metabolic tracers, 15 transaxial planes of 6.75-mm width were obtained using a whole body positron emission tomographic scanner (Siemens/CTI 931). The transaxial image data were realigned to generate images in short-, vertical- and horizontal long-axis views. Corresponding images of myocardial perfusion and F-18 deoxyglucose uptake in five myocardial segments (anterior, lateral, inferior, septum and apex) were visually compared by two observers who did not know the clinical data of the patients.

Patients were categorized on the basis of visual evaluation of regional blood flow and F-18 deoxyglucose uptake. A scintigraphic pattern of *match* was defined as an area of decreased blood flow and F-18 deoxyglucose uptake involving at least one left ventricular segment, whereas a pattern of *mismatch* was defined as an area of decreased blood flow and relatively increased F-18 deoxyglucose uptake based on a regional scoring system involving at least one segment (17). Coexistence of left ventricular segments with a match and a mismatch pattern in a patient was considered as a mismatch.

Revascularization. Forty patients underwent successful coronary revascularization, although one patient had a postoperative cardiac arrest and required placement of an artificial heart. Six of the 40 patients underwent coronary angioplasty and 34 underwent coronary artery bypass grafting.

Data acquisition. Information obtained from the charts included patient age, indication for and date of positron emission tomographic scan, indication for and date of revascularization, the number of vessels with >70% stenosis, cardiac risk factors (including family history of coronary artery disease, >10 pack-year smoking history, hypercholesterolemia, hypertension, diabetes mellitus, male gender and peripheral vascular occlusive disease), left ventricular function by cardiac catheterization or radionuclide ventriculography, New York Heart Association functional classification for symptoms of congestive heart failure (18) and Canadian Cardiovascular Society classification for angina (19).

Patient grouping. The patients were classified into one of four groups as a function of the positron emission tomographic result and performance or nonperformance of subsequent revascularization. Group A comprised 18 patients with one or more left ventricular segments with reduced blood flow and preserved F-18 deoxyglucose uptake (mismatch) on positron emission tomographic imaging who did not undergo subsequent revascularization. Group B comprised 26 patients with a mismatch on positron emission tomography who underwent subsequent revascularization. Group C comprised 24 patients with no mismatch on positron emission tomography who did not undergo revascularization. Group D comprised 14 patients with no mismatch who underwent subsequent revascularization. The 18 patients in group A did not undergo revascularization for the following reasons: refusal of surgery (2 patients including 1 with unsuccessful coronary angioplasty), pending planned coronary artery bypass grafting (5 patients) and physician judgment that the patient was appropriately managed medically (10 patients).

Follow-up. Patients were interviewed by telephone an average of 12 months after the positron emission tomographic imaging procedure. Information obtained from the interview by a physician (D.E.) included current New York Heart Association and Canadian Cardiovascular Society classification for congestive heart failure and angina, respectively, subsequent myocardial infarction, death or need for

Table 1. Events on Follow-Up: Death, Myocardial Infarction, Cardiac Arrest and Late Revascularization

	Group A (MM^+, RV^-)	Group B (MM^+, RV^+)	Group C (MM^-, RV^-)	Group D (MM^-, RV^+)
Subjects (no.)	18	26	24	14
Events				
No.	9	3	3	1
Rate	0.5	0.12	0.13	0.07
Type				
Death	6	1	2	. . .
MI	3	. . .	. . .	. . .
Cardiac arrest	. . .	1	. . .	. . .
Late revascularization	. . .	1	1	1

There was a significant difference in the proportion of events between the groups: ($\chi^2 = 11.43$, $p < 0.01$) and between the proportion of events in group A and that in each of the other groups ($p < 0.01$). MI = myocardial infarction; MM^+ and MM^- = match or no mismatch on positron emission tomography; RV^+ and RV^- = revascularization and no revascularization.

urgent revascularization because of new symptom development. An event was defined as death, myocardial infarction, cardiac arrest or late revascularization because of development of new symptoms. The diagnosis of myocardial infarction required increased total serum creatine kinase with >5% fraction of myosin-specific enzyme bands in the appropriate clinical setting.

Statistical analysis. Values are presented as mean value ± 1 SD. Event frequency and improvement in functional status among the four groups were analyzed by chi-square test. Group characteristics were compared by using a one-way analysis of variance (ANOVA) test and Scheffé analysis for multiple comparisons. A p value < 0.05 was considered significant.

Results

Patient characteristics. The 82 patients in the final study group had a mean age of 59 ± 10 years. The mean left ventricular ejection fraction as determined by radionuclide ventriculography was 34 ± 13%, the mean number of risk factors was 4.0 ± 1.0, the mean number of stenosed vessels was 2.1 ± 0.8, the mean congestive heart failure functional class was 1.8 ± 0.8 and the mean angina class was 1.9 ± 0.7. Seventy-two men and 10 women were studied.

Events (Table 1). The 82 patients entered into the study had 16 identified events: 9 deaths, 3 myocardial infarctions, 1 cardiac arrest and 3 late revascularizations. The average time from positron emission tomographic imaging to an event was 5 ± 5 months for group A, 6 ± 6 months for group B, 13 ± 10 months for group C and 6 months for group D. The 18 patients in group A (evidence of jeopardized myocardium on positron emission tomography, revascularization not performed) had nine events (50% event rate) including six deaths and three myocardial infarctions. Four of these deaths were attributed to acute myocardial infarction; one death of probable cardiac origin occurred during a hospital admission for a bleeding peptic ulcer and one occurred suddenly in the postoperative period after placement of an internal defibrillator. The 26 patients in group B (evidence of jeopardized myocardium on positron emission tomographic imaging, revascularization performed) had three events (11.5% event rate) including one death, one perioperative cardiac arrest and one late revascularization. The patient with perioperative arrest received an artificial heart and subsequently underwent successful human allograft transplantation. The death in this group was attributed to severe congestive heart failure. The 24 patients in group C (no evidence of jeopardized myocardium, revascularization not performed) had three events (12.5% event rate) including two deaths and one late revascularization. One death was attributed to acute myocardial infarction and one to severe left ventricular failure. The 14 patients in group D (no evidence of jeopardized myocardium, revascularization performed), had one event, a late revascularization (7.1% event rate). There was a significant difference in the proportion of events between the groups ($\chi^2 = 11.43$, $p < 0.01$) (Table 1). When group A was tested against each of the other three groups, the results of each test were significant ($p < 0.01$); thus the event rate in group A was greater than the event rate of the other groups.

Group characteristics (Table 2). The patients in each group were similar with regard to age, left ventricular ejection fraction, number of stenosed coronary arteries, number of risk factors and congestive heart failure classification. The mean angina class was higher in group B (2.5 ± 0.9) than in the other groups ($p < 0.05$). These clinical variables did not differ significantly between the patients who did or did not have an event.

Functional classification (Table 3). The functional class of all patients with respect to congestive heart failure and angina was assessed at the time of the positron emission tomographic scan and at an average of 12 months of follow-up. Only patients who did not have an event were analyzed for change in functional status. The proportion of subjects in each group who experienced improvement of at least one

Table 2. Group Characteristics: Scintigraphic Groups A Through D and Groups With and Without Subsequent Events

	Scintigraphic Groups					Groups With and Without Subsequent Events		
	Group A (MM^+, RV^-) (n = 18)	Group B (MM^+, RV^+) (n = 26)	Group C (MM^-, RV^-) (n = 24)	Group D (MM^-, RV^+) (n = 14)	p Value	With Events (n = 16)	Without Events (n = 66)	p Value
Age (yr)	61 ± 8	59 ± 11	59 ± 10	56 ± 9	0.65	62 ± 7	58 ± 10	0.80
LVEF (%)	33 ± 11	36 ± 13	32 ± 16	37 ± 12	0.63	31 ± 14	34 ± 13	0.74
Stenosed vessels (no.)	1.9 ± 0.8	2.0 ± 0.8	2.2 ± 0.8	2.1 ± 0.6	0.94	1.9 ± 0.8	1.6 ± 0.8	0.88
Risk factors (no.)	4.3 ± 1.4	3.9 ± 1.0	3.9 ± 0.8	4.2 ± 0.7	0.45	4.5 ± 1.2	3.9 ± 0.9	0.22
NYHA CHF class	1.8 ± 0.7	1.8 ± 0.9	2.0 ± 0.9	1.7 ± 0.8	0.85	1.7 ± 0.8	1.8 ± 0.8	0.91
CCS angina class	2.1 ± 0.7	2.5 ± 0.9	1.2 ± 0.4	1.9 ± 0.8	<0.05	2.3 ± 0.8	1.9 ± 0.8	0.10

Unless otherwise indicated, values are expressed as mean value ± SD. CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; other abbreviations as in Table 1.

class was compared by chi-square analysis. More patients in group B (mismatch, revascularization) than in the other groups had improvement in anginal and congestive heart failure class ($\chi^2 = 23.2$, $p < 0.001$, respectively).

Discussion

Identification of patients likely to benefit from coronary revascularization. Our results indicate that positron emission tomography in combination with F-18 deoxyglucose provides prognostic information in patients with severely impaired left ventricular function. The presence of metabolically compromised myocardium, as defined by decreased myocardial perfusion and relatively enhanced F-18 deoxyglucose uptake, identified a subgroup of patients who had a significantly higher rate of cardiac complications in the absence of coronary revascularization than that of patients with similar positron emission tomographic findings and subsequent revascularization or patients without evidence of metabolically compromised myocardium. The observation that left ventricular function, extent of coronary artery disease and functional class at baseline, with the exception of greater severity of angina in group B, did not differ among these groups suggests that positron emission tomography may provide, independently from the established prognostic markers, clinical information important for further management. It may be uniquely suited to identify subgroups of patients with impaired left ventricular function who are likely to benefit from coronary revascularization.

Each year in the United States >400,000 patients undergo coronary bypass surgery or coronary transluminal angioplasty (20). Although symptomatic and prognostic benefits from coronary artery revascularization appear to extend to a large number of patients, several multicenter studies (21–23) performed in the 1970s demonstrated that surgery resulted in increased longevity only in patients with left main coronary artery disease or multivessel coronary artery disease with impaired left ventricular function. A more recent evaluation of medical versus surgical therapy based on the Duke University experience (1969 to 1984) found the results of surgical therapy to have improved with time (24). By 1984, these investigators found surgical therapy to have superior survival benefit for most patient subgroups. Although these positive results for surgical revascularization are well appreciated, especially in patients with advanced coronary artery disease, patients with prior myocardial infarction and severely impaired left ventricular function are at higher risk for perioperative complications (25,26). In addition, an increasing number of patients with previous coronary bypass surgery suffer from progression of coronary artery disease and require a second or third surgical revascularization. These procedures are technically more difficult and are associated with higher risk than that of the initial revascularization. Advances in surgical technique, including the use of improved intraoperative cardioplegic protection of ischemic myocardium, enhances the surgical success rate in patients with severely impaired left ventricular function and allows the performance of surgery in patients previously considered to be unsuitable candidates for revascularization (24,27).

Differentiation between scar tissue and hibernating or stunned myocardium. Regional impairment of left ventricular function in patients with ischemic heart disease does not necessarily represent scar tissue, but may be a result of hibernating or stunned myocardium (28,29). Previous studies using nonsurgical and surgical revascularization have indi-

Table 3. Subjects With Improvement by One or More Functional Classes

	Group A	Group B	Group C	Group D	Chi-Square	p Value*
CCS angina	0	19	0	7	23.6	<0.001
NYHA CHF	0	8	3	4	23.2	<0.001

*The p value reflects the statistically higher incidence of improvement in group B. Abbreviations as in Table 2.

cated that both regional and global left ventricular function can dramatically improve after revascularization in subsets of patients with impaired function. However, functional recovery can occur only in reversibly injured and, hence, viable myocardium. On the basis of this assumption, major research efforts have concentrated on the development of techniques that provide noninvasive markers for tissue viability. Several studies (30) indicate that neither the degree of regional wall motion impairment seen on echocardiography nor the reduction in rest myocardial blood flow adequately differentiates scar tissue from hibernating myocardium. Thallium-201 scintigraphy has been proposed (31,32) for the detection of compromised myocardium by evaluating thallium-201 redistribution within exercise-induced perfusion defects. However, the specificity of this scintigraphic pattern has been challenged recently by several investigations (33–36) that demonstrated functional recovery in segments with nonredistributing thallium-201 defects.

Prognostic role of positron emission tomography. This study is the first to examine the prognostic role of positron emission tomography in patients with advanced coronary disease considered to be candidates for revascularization. Our results suggest that, in addition to the predictive value of F-18 deoxyglucose uptake for tissue recovery, important prognostic information can be obtained from metabolic imaging in patients not undergoing revascularization. In the relatively small number of patients studied, the presence of left ventricular segments with decreased myocardial perfusion but maintained metabolic activity, as assessed with F-18 deoxyglucose, was associated with high risk for cardiac events. This group of 18 patients experienced six cardiac deaths and three myocardial infarctions within the 1st 12 months of the study. Conventional markers for cardiac risk, such as left ventricular ejection fraction and extent of coronary artery disease, did not differ significantly between this group and the other three patient groups. Therefore, evidence of metabolically jeopardized myocardium may independently identify a pathophysiologically unstable situation that is associated with future cardiac complications such as arrhythmias or myocardial infarction, or both. These data represent further validation of metabolic imaging as a specific marker for jeopardized tissue in the human heart.

The clinical outcome of patients with concordantly decreased perfusion and metabolic activity in segments with previous infarction was similar in those who did or did not undergo revascularization. Our study group may have been too small to detect a difference in outcome, which would be expected from previous studies in similar patients. However, as assessed by anginal symptoms, our patient group, like those in previous studies, did seem to benefit from revascularization. Because positron emission tomographic metabolic imaging is performed in the rest state, it may not have detected myocardium at risk that would be detected by stress testing. This factor could account for the small degree of improvement of symptoms and reduction of risk for events that occurred with revascularization. Cardiac stress testing was not included in this analysis. Stress-induced ischemia may be an independent factor affecting prognosis in these patients. Further studies are required to elucidate the possible beneficial effects of revascularization in patients with severely impaired left ventricular function but without metabolic evidence of compromised myocardium.

Technical considerations. Our study is a retrospective evaluation of clinical positron emission tomographic viability studies. Although care was taken to identify all possible factors influencing the choice of therapy, a selection bias not represented by such variables as left ventricular ejection fraction and extent of coronary artery disease may have partly contributed to the greater incidence of cardiac events in patients not undergoing revascularization. In addition, the results of the positron emission tomographic scans were known to the physicians selecting patient treatment and this knowledge may have influenced their choice in some patients. Because such selection bias is expected to increase the rate of surgery in patients with a mismatch positron emission tomographic pattern—and hence to decrease the likelihood of complications in this group—the presence of such bias would strengthen the significance of our findings. This first report on the prognostic information provided by positron emission tomography requires confirmation in a larger number of patients, optimally with use of a prospective multicenter study. However, our initial observations may provide the basis for improved selection of patients with impaired left ventricular function for revascularization.

Our study did not include a comparison of positron emission tomography and thallium-201 scintigraphy in these patients. To our knowledge, no similar study has been performed with thallium-201 scintigraphy and it is possible that thallium-201 redistribution patterns identify high risk patients with similar prognostic power. However, our experience indicates that positron emission tomography in combination with F-18 deoxyglucose appears to provide higher image quality than does thallium-201 scintigraphy, especially in patients with severely impaired left ventricular function and inability to undergo exercise testing. Future studies employing technetium-99m–labeled blood flow tracers, which provide improved image quality, are required to examine the prognostic value of conventional nuclear imaging procedures for the detection of jeopardized myocardium. Positron emission tomography is associated with a higher cost than that of conventional scintigraphic techniques. However, the benefit/cost ratio of this advanced imaging technology may be justified on the basis of higher diagnostic and prognostic performance if costs of subsequent therapy and interventions are taken into account.

Conclusions. Positron emission tomography in combination with F-18 deoxyglucose provides important clinical information in patients with advanced coronary artery disease and severely impaired left ventricular function. Comparative studies with thallium-201 scintigraphy suggest that positron emission tomography is the most accurate noninvasive technique currently available to identify viable but compromised myocardium. Previous data have documented its high predictive value for recovery of regional function relative to that of other techniques. This study provides the first data on the prognostic implications of relative increased F-18 deoxyglucose uptake in segments with decreased myocardial perfusion. Metabolic imaging with positron emission tomography may provide important information guiding the management of patients with ischemically compromised myocardium.

These data indicate that patients with severely impaired function and metabolic evidence of jeopardized myocardium are at high risk for cardiac events. If such patients cannot undergo revascularization, either aggressive medical therapy or evaluation for cardiac transplantation may be necessary to reduce the risk of subsequent complication. However, patients without metabolic evidence of jeopardized myocardium had a similar rate of complications whether or not revascularization was performed. Thus, positron emission tomography may be particularly useful for selecting patients with higher perioperative risk for necessary surgical and nonsurgical revascularization. Additional studies are required to confirm the results of this study and to define the prognostic performance of positron emission tomographic performance in comparison with that of other markers of tissue viability with consideration of benefit/cost ratios.

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